Scientific Abstract: Development of Effective Immunotherapy for Prostate Cancer Patients: Phase I/II Study of Human GM-CSF Gene-Transduced Irradiated Prostate Allogeneic Cancer Cell Vaccines (Allogeneic Prostate GVAX®) in Advanced Prostate Cancer Patients made Lymphopenic by Chemotherapy and Infused with Autologous Peripheral Blood Mononuclear Cells. (Providence IRB #02-119, BB-IND 11716)

Recent work by several groups has shed new light on the processes that regulate T cell expansion in vivo. It is now appreciated that naïve T cells, which normally do not proliferate, or do so at a very slow rate, are driven to expand rapidly when they are transferred into lymphopenic hosts. The self-peptides bound by host MHC class I and class II molecules not only control T-cell survival, but also induce homeostasis-driven proliferation (lymphopenia-driven proliferation) of both the CD4 and CD8 T-cells in the periphery of T-cell deficient hosts. Since reconstitution of the T-cell compartment in lymphopenic hosts is regulated by the peptides occupying MHC class I and II molecules at the time of T cell recovery, we considered that these mice might also be "hypersensitive" to tumor antigens presented by APC. To test this hypothesis we vaccinated lymphopenic mice with a melanoma or prostate cancer vaccine following intravenous reconstitution with naïve spleen cells and 8 days later examined the tumor vaccine-draining lymph node (TVDLN) T cells for tumor-specific activity and therapeutic efficacy in adoptive transfer studies. This strategy has increased the effectiveness of vaccination against weakly and poorly immunogenic tumors, and when combined with a GM-CSF secreting vaccine and adoptive transfer of tumor vaccine-draining lymph node (TVDLN) T cells, it results in regression of a previously untreatable murine prostate cancer. We extended these studies to show that this strategy of reconstituting lymphopenic mice (RLM) with spleen cells could be used to augment the development of a protective immune response in the weakly immunogenic B16-F10 melanoma model. These data document that this novel vaccination strategy can significantly augment the therapeutic activity of a tumor vaccine. Additionally, a clinical trial in which we vaccinated prostate cancer patients with two allogeneic prostate cancer cell lines, PC3 and LNCaP, that were transduced with the cDNA encoding GM-CSF (Allogeneic Prostate GVAX™), found an increase in progression-free survival of patients with metastatic disease treated at the highest dose level. Encouraged by the finding of some antitumor efficacy in this clinical trial, we plan to determine whether vaccination of patients during lymphopenia will induce homeostatic proliferation and result in higher frequencies of tumor-specific T cells. The proposed clinical trial is modeled directly from the preclinical studies.

The objectives of this proposal are: (1) To evaluate the safety of combined Allogeneic Prostate GVAX™ vaccination, chemotherapy with cyclophosphamide +/- fludarabine and hematopoietic reconstitution in patients with advanced hormone refractory prostate cancer (HRPC). (2) To explore the effects of different chemotherapy regimens on the immune response of Allogeneic Prostate GVAX™ vaccinated and reconstituted lymphopenic patients with HRPC. (a) Compare the frequency of tumor vaccine-specific T cells in Cohorts A-C; (b) compare the frequency of PSMA-specific T cells in Cohorts A-C; (c) compare the titer of vaccine-specific antibodies in Cohorts A-C. (3) To evaluate in vitro sensitization (IVS) methods for their capacity to expand tumor vaccine-specific CD4+ and CD8+ T cells from the peripheral blood and to determine whether the degree of lymphopenia inversely correlates with the expansion of tumor-specific CD4 and CD8 T cells. The primary objectives of the clinical protocol are the same as the first two specific aims of the grant. The secondary objective is: To evaluate the combination of allogeneic Prostate GVAX™ and chemotherapy for antitumor effectors based on reducing serum PSA levels and changes in bone scans or measurable disease.